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Synthesis, characterization and antimicrobial activity of Cu(II), Co(II), Ni(II) and Zn(II) complexes derived from 1-(pyridin-2-yl aminomethyl) pyrrolidine-2,5-dione and 1-phenyl(pyridin-2-yl aminomethyl) pyrrolidine-2,5-dione

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ABSTRACT

Complexes of Cu(II), Ni(II), Co(II) and Zn(II) have been synthesized using the Mannich base formed by the condensation of 2-amino pyridine, formaldehyde /benzaldehyde and succinimide. Microanalysis, molar conductance, magnetic susceptibility, IR, UV-Vis, ^{1}H NMR, ^{13}C NMR studies have been carried out to determine the structure of the complexes. From the data, it is found that all the complexes possess octahedral geometry. All the title complexes were screened for antimicrobial activity by the well diffusion technique using DMSO as solvent. The minimum inhibitory concentration (MIC) values were calculated at 37°C for a period of 24 h. It has been found that all the complexes are antimicrobial active and show higher activity than the free ligand.

KEYWORDS

Complexes;
Mannich base;
Complexes;
Spectra;
DMSO;
Minimum inhibitory concentration.

INTRODUCTION

Coordination complexes are gaining increasing importance in recent years particularly in the design of repository; slow release or long acting drugs in nutrition and in the study of metabolism[1]. The metal ions are also known to accelerate drug action. Transition metals are essential for the normal functioning of living organisms. Therefore, it is not surprising that transition metal coordination compounds are of great interest as potential drugs[2-5]. A general study of the structural and bonding features of the various Mannich base complexes can help better understanding of the complex life processes. The findings of structural studies are interesting in that the Mannich base ligands can control the stereochemistry of the complexes and provide us with numerous examples of unusual geometries about the central metal ion. Therefore, they can serve to illustrate the coordination flexibility of these ions.

A wide number of papers report the synthesis and characterization of many metal complexes of Mannich bases derived from amino pyridine. It is well known from the literature that amino pyridine compounds containing the amine moiety have a strong ability to form metal complexes[6]. Succinimide is continued to attract considerable attention from theoretical standpoints concerning the mode of bonding and its general reactivity as coordinated ligand. Keeping the above facts in mind

and in continuation of our earlier work on transition metal complexes with Mannich bases[7], the present paper describes the synthesis and characterization of Cu(II), Ni(II), Co(II) and Zn(II) complexes with the biologically important Mannich base.

The Mannich reaction is employed in the organic synthesis of natural compounds like for instance Peptides-Nucleotides-Antibiotics and Alkaloids. The Mannich Reaction is also used in the synthesis of medicinal compounds e.g. Rolitetracycline (Mannich base of Tetracycline), Fluoxetine (Antidepressant) and Tolmetin (Anti-inflammatory drug).

The Mannich reaction is a three component condensation in which a compound containing an active hydrogen atom is allowed to react with an aldehyde or ketone and a primary or secondary amine with concomitant release of water to produce a base known as Mannich base, in which the active hydrogen is replaced by an aminomethyl group[13,14]. The formation of both C-C and C-N bond in this aminomethylation process makes the Mannich reaction an extremely useful synthetic transformation. Mannich bases have wide application in the area of pharmaceuticals and macromolecular chemistry[15]. Some Mannich bases have antimalarial, antiviral properties while some other act as antihistamines, anti-inflammatories and antimicrobials. The present work is undertaken in an attempt to synthesize some new Mannich bases of succinimides.

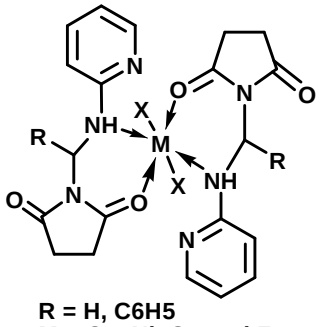
EXPERIMENTAL

Preparation of 1-(pyridin-2-yl amino)methy pyrrolidine-2,5-dione (SFAP)

2-aminopyridine (9.50g, 0.1mol) and succinimide (9.09g, 0.1mol) were dissolved in minimum amount of distilled water and the contents were mixed well at room temperature until a clear solution was obtained. (10mL, 0.1mol) of formaldehyde was added to this mixture. After 10 days a brownish solid product (Figure 5) was obtained and it was washed with distilled water several times and dried in the air oven at 80°C and recrystallized from hot ethanol by slow evaporation method.

Preparation of 1-phenyl(pyridin-2-yl aminomethyl) pyrrolidine-2,5-dione (SBAP)

2-aminopyridine (9.50g, 0.1mol) and succinimide



R = H, C6H5
M = Cu, Ni, Co and Zn
X = Cl, NO3

Figure 1 : Structure of the complex

(9.09g, 0.1mol) were dissolved in minimum amount of distilled water and the contents were mixed well at room temperature until a clear solution was obtained. (10mL, 0.1M) of benzaldehyde was added to this mixture. After 10 days a brownish solid product was obtained and it was washed with distilled water several times and dried in the air oven at 80°C and recrystallized from hot ethanol by slow evaporation method.

Materials and methods

The chemicals used in the synthesis were obtained from Aldrich Chemical Company and were used without further purification. The solvents used were of spectroscopic grade. IR spectra were recorded on a Perkin-Elmer FTIR spectrophotometer in KBr. ^{1}H NMR spectra were recorded on a Bruker Advance DPX 300 MHz Ultra-Shield FTNMR Spectrophotometer in DMSO-d_6 and $CDCl_3$ with TMS as internal reference. Chemical shifts are expressed in δ units (ppm). Ultraviolet-visible (UV-Vis) absorption spectra were recorded on Perkin-Elmer Spectrophotometer (EZ 301) at the wavelength of maximum absorption (λ_{max}) in dimethylsulfoxide (DMSO) / dimethylformamide (DMF). All melting points were taken in open capillary tubes in °C by using Elico instrument and mass spectra on a LUNA instrument. The micro-elemental results were obtained on a Vario-EL instrument. The human pathogenic bacterial species (*Pseudomonas aeuroginosa*, *Escherichia coli*, *Salmonella typhi*, *bacillus cereus*, *and klebsilla pneumonia*) were used for the anti microbial studies.

Microbial inoculums preparation

The young microbial inoculums/culture was prepared and used in the entire research period. The nutri-

TABLE 1 : Physical characterization, analytical, molar conductance and magnetic susceptibility data of the ligand and its complexes

Compound	Color	Contents (found/calcd) %					Λ_m Ohm^{-1} cm^2 mol^{-1}	μ_{eff}, μ_B
		Metal	C	H	N	O		
Ligand-SFA	Brown	-	58.56	5.42	20.47	15.55	---	---
SFA- $CuCl_2$	Dark green	11.66	44.09	4.07	15.42	11.75	12.6	1.89
SFA -$NiCl_2$	Lightgreen	10.87	44.48	4.11	15.56	11.85	11.3	2.81
SFA -$CoCl_2$	Brown	10.91	44.46	4.10	15.56	11.85	11.1	4.77
SFA-$ZnCl_2$	Colorless	11.96	43.94	4.06	15.37	11.71	10.2	---
SFA-$Cu(NO_3)_2$	Dark green	10.63	40.17	3.71	18.74	26.76	12.1	1.80
SFA-$Ni(NO_3)_2$	Light green	9.90	40.50	3.74	18.89	26.97	12.0	2.66
SFA-$Co(NO_3)_2$	Brown	9.93	40.48	3.74	18.88	26.96	11.9	4.70
SFA-$Zn(NO_3)_2$	Colorless	9.93	40.48	3.74	18.88	26.96	10.2	---
Ligand-SBA	Brown	-	68.33	5.38	14.93	11.35	---	---
SBA-$CuCl_2$	Dark green	9.12	55.14	4.34	12.06	9.18	11.1	1.77
SBA-$NiCl_2$	Light green	8.48	55.52	4.37	12.14	9.25	11.8	2.83
SBA-$CoCl_2$	Brown	8.51	55.50	4.37	12.14	9.24	10.9	4.72
SBA-$ZnCl_2$	Colorless	9.36	54.99	4.33	12.02	9.16	10.7	---
SBA- $Cu(NO_3)_2$	Dark green	8.47	51.23	4.03	14.94	21.33	11.8	1.72
SBA-$Ni(NO_3)_2$	Light green	7.87	51.57	4.06	15.03	21.47	11.2	2.68
SBA-$Co(NO_3)_2$	Brown	7.90	51.55	4.06	15.03	21.46	10.2	4.60
SBA-$Zn(NO_3)_2$	Colorless	8.70	51.11	4.02	14.90	21.27	10.0	---

---- = No activity, No minimum bactericidal concentration (MBC)

ent broth (NB) for bacteria and potato dextrose broth (PDB) for fungi were prepared and poured into tubes and sterilized. The pure microbial cultures collected were inoculated in the tubes using inoculation needles and loops. Then these tubes were incubated at different temperatures and time duration (at 37°C and 24-48 hours for bacteria and at 27°C and 48-72 hours for fungi). 20mg of synthesized organic compounds dissolved in 2ml of DMSO were used as a stock solution. From the stock solution, various concentrated discs (20, 40 and 60 μg) were prepared.

1-(pyridin-2-yl amino)methyl pyrrolidine-2,5-dione (SFAP)

M.F: $C_{10}H_{11}N_3O_2$, Yield: 82%, m.p. 117-118°C, Mol.wt: 205.21. FT-IR KBr ν in cm^{-1}: 3461 (NH), 3059, 3030 (Ar-CH), 1699 (C = O), 1600 (C = C), 1191, 1153 (C-N-C). ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.61 (s, 4H, $(CH_2)_2$), 3.34 (s, NH), 6.63-8.00 (pyridine ring m, 4H). ^{13}C NMR (300 MHz DMSO-d_6) δ 28.17 (s, 2C, $(CH_2)_2$), 46.68 (s, 1C, CH_2), 106.81 (s, C), 114.66-156.59 (m, 5C pyridine ring), 177.17 (s, 2C, C = O). FABMS (positive mode) m/z: 205.21 ($C_{10}H_{11}N_3O_2$); 127.03 ($C_5H_7N_2O_2^{\cdot+}$); 107.13 ($C_6H_7N_2^{\cdot+}$); 98.07 ($C_4H_4NO_2^{\cdot+}$); 93.10 ($C_5H_5N_2^{\cdot+}$); 78.09 ($C_5H_5N^{\cdot+}$). Calculated: C 58.53%, H 5.40%, N 20.48%, O 15.59%. Found: C 58.61%, H 5.46%, N 20.42%, O 15.51%.

1-phenyl(pyridin-2-yl amino methyl) pyrrolidine-2,5-dione (SBAP)

M.F: $C_{16}H_{15}N_3O_2$, Yield: 78%, m.p. 102-103°C, Mol.wt: 281.31. FT-IR KBr ν in cm^{-1}: 3370 (NH), 3174, 3020 (Ar-CH), 1692 (C = O), 1575 (C = C), 1220, 1185 (C-N-C), 778, 707 (mono substituted benzenoid ring). ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.89 (s, 4H), 3.34 (s, NH), 7.29-7.42 (m, 5H), 7.43-8.07 (m, 4H, pyridine ring). ^{13}C NMR (300 MHz, DMSO-d_6) δ 28.11 (s, 2C, $(CH_2)_2$), 61.72 (s, 1C, CH), 108.53 (s, C), 113.57-178.19 (m, 10C, benzyl & pyridine ring), 192.44 (s, 2C, C = O). FABMS (positive mode) m/z: 281.31 ($C_{16}H_{15}N_3O_2$); 203.22 ($C_{11}H_{11}N_2O_2^{\cdot+}$); 183.22 ($C_{12}H_{11}N_2^{\cdot+}$); 106.12 ($C_7H_7N^{\cdot+}$); 97.91 ($C_4H_4NO_2^{\cdot+}$); 89.10 ($C_7H_6^{\cdot+}$). Calculated: C 68.31%, H 5.37%, N 14.94%, O 11.37%. Found: C 68.39%, H 5.29%, N 14.99%, O 11.33%.

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TABLE 2 : Anti bacterial activity zone of inhibition in MM

Complexes	ST	KP	EC	BC	PA
Streptomycin	29	26	33	23	30
SFAP-$CuCl_2$	----	----	----	----	----
SFAP-$Cu(NO_3)_2$	4	----	----	----	----
SFAP-NiCl2	16	4	----	----	----
SFAP- $Ni(NO_3)_2$	----	----	----	----	----
SFAP-$CoCl_2$	12	----	4	----	18
SFAP-$Co(NO_3)_2$	10	4	----	----	----
SBAP-$CuCl_2$	12	8	----	12	20
SBAP- $Cu(NO_3)_2$	----	7		----	----
SBAP-$NiCl_2$	----	----	----	----	----
SBAP-$Ni(NO_3)_2$	----	----	----	----	----
SBAP-$CoCl_2$	22	13	15	16	----
SBAP-$Co(NO_3)_2$	----	10	20	4	15
DMSO	----	----	----	----	----

---- = No activity, No minimum bactericidal concentration (MBC)

RESULTS AND DISCUSSION

Physical characteristics, micro analytical and magnetic susceptibility data of the complexes are given in TABLE 1. The analytical data of all the complexes correspond to the general formula $M(L)_2$. Magnetic susceptibility values of the complexes at room temperature are consistent with octahedral geometry around the central metal ions. The chelates show no appreciable conductance, and this supports the hypothesis of their neutral nature.

The electronic absorption spectra of the ligand and its complexes are recorded in a DMSO solution. The Co(II) complexes (d_7) exhibits two bands having λ_{max} at 306 and 788nm. The first band assigned to the π-π^* transition of the >C = N as a result of complexes formation. The next band can be assigned to $^4T_{1g}(F) \rightarrow {}^4A_{2g}(F)$ which reveals the octahedral geometry of the ligand around the Co^{2+} ion. The magnetic moment of the Co(II) complexes (4.60-4.77μ_B) suggests the high spin six coordinated octahedral arrangement of the ligand molecule around the metal ion. The spectrum of the Ni(II) complexes (d_8) exhibits four bands having λ_{max} at 300, 377, 759, and 798nm. The first two bands assigned to the π-π^* transition of the >C = N and the ligand-to metal ion charge-transfer band (L $\rightarrow$Ni) as a result of complexes formation. The last two bands ν_1 and ν_2 can be assigned to $^3A_{2g}(F) \rightarrow {}^3T_{1g}(P)$[14] and

TABLE 3 : Antibacterial study of investigated compounds (MIC$\times 10^{-2}$ mol/L)

Complexes	MIC(µG/ML)	MBC(µG/ML)
SFAP-$Cu(NO_3)_2$	ST – 12.5	----
SFAP-$NiCl_2$	ST- 3.125	6.25
SFAP-$NiCl_2$	KP -6.25	---
SFAP- $Ni(NO_3)_2$	ST- 6.25	---
SFAP- $Ni(NO_3)_2$	KP- 12. 5	---
SFAP-$CoCl_2$	ST- 1.56	---
SFAP-$CoCl_2$	EC-12.5	---
SFAP-$CoCl_2$	PA- 3.125	6.25
SFAP-$Co(NO_3)_2$	ST – 6.25	12.5
SFAP-$Co(NO_3)_2$	KP- 12.5	---
SBAP- $Cu(NO_3)_2$	KP- 4.5	---
SBAP-$CuCl_2$	ST – 4.25	---
SBAP-$CuCl_2$	KP-5.5	---
SBAP-$CuCl_2$	BC-1.5	---
SBAP-$CuCl_2$	PA-3.12	---
SBAP-$CoCl_2$	ST- 1.56	---
SBAP-$CoCl_2$	KP- 12.5	---
SBAP-$CoCl_2$	EC-6.25	12.5
SBAP-$CoCl_2$	BC-1.525	3.125
SBAP-$Co(NO_3)_2$	KP -3.125	---
SBAP-$Co(NO_3)_2$	EC-3.125	6.25
SBAP-$Co(NO_3)_2$	BC 6.25	----
SBAP-$Co(NO_3)_2$	PA 3.125	6.25

---- = No activity, No minimum bactericidal concentration (MBC)

$^3A_{2g}(F) \rightarrow {}^3T_{1g}(F)$, respectively. This indicates an octahedral geometry around the Ni^{2+} ion. This arrangement is supported by its magnetic moment value (2.83-2.66μ_B). The Cu^{2+} ion exhibits a broad asymmetry band around 535nm attributed to $^2B_{1g} \rightarrow {}^2A_{1g}$ transition similar to octahedral arrangement, which is supported by its magnetic moment value (1.89 -1.72μ_B). No transitions were observed in the visible region for the Zn(II) complexes consistent with the d_{10} configuration of the Zn^{2+} ion. This complexes is also found to be diamagnetic as expected for the d_{10} configuration.

All the complexes are stable at room temperature, non-hygroscopic, insoluble in water, soluble in methanol, ethanol, DMF, DMSO and chloroform. The analyses of the complexes are consistent with the stoichiometry proposed and are summarized in TABLE 1. All the complexes have low conductance values, which indicate that the complexes are nonelectrolytic in nature.

TABLE 4 : Anti fungal activity zone of inhibition in MM

Compound	A.O	A. F
Ampotericin B	20	16
SFAP	----	----
SBAP	12	----
SFAP-$CuCl_2$	4	6
SFAP-$Cu(NO_3)_2$	3	6
SFAP-NiCl2	----	----
SFAP- $Ni(NO_3)_2$	----	----
SFAP-$CoCl_2$	3	----
SFAP-$Co(NO_3)_2$	4	4
SBAP-$CuCl_2$	2	----
SBAP- $Cu(NO_3)_2$	----	----
SBAP-$NiCl_2$	----	----
SBAP-$Ni(NO_3)_2$	----	----
SBAP-$CoCl_2$	18	12
SBAP-$Co(NO_3)_2$	10	8
DMSO	----	----

---- = No activity, No minimum bactericidal concentration (MBC)

The mass spectrum of the ligand shows a peak at m/z = 205.21 and 281.31 respectively corresponding to the molecular ion peak, and its copper complexes exhibits the peak at m/z = 731.37 corresponding to the molecular mass of the proposed structure for the copper complexes. It indicates the $[MLX_2]$ stoichiometry for the complexes. This stoichiometry is also supported by the mass spectra of the other complexes. The C = O stretching frequencies, in complexes are significantly lower than C = O in the corresponding ligands. The IR spectrum of the ligand shows a $\nu(C = O)$[15] band at 1699 and 1692cm^{-1}. The IR spectrum of the ligand shows ν(N-H) bands around 3461–3020cm^{-1} and also it is shifted by 15-20cm^{-1} to the lower energy region in the complexes compared to the free ligand. This phenomenon appears to the coordination of the succinimide oxygen and amino pyridine amine nitrogen to the metal ion. The (ν_{M-N}) bands appear around 400-450cm^{-1} indicating the coordination to the metal ion. Below 800 some new bonds appeared, and these were tentatively assigned as metal-oxygen bond formation (ν_{M-O}).

These bands remain almost intact in the spectra of the complexes showing their nonparticipation in the chelation; however, displacement in these frequencies is due to the increased positive charge on the N atom by the donation of an electron pair. The ^{1}H NMR spectra of the Mannich base and its zinc complexes were recorded in DMSO at room temperature. The samples were prepared by dissolution in DMSO and the chemical shifts were recorded with respect to TMS. The ^{1}H NMR spectrum of the ligand investigation shows a signal at 8.9 ppm, which is assigned to the NH proton in the amine moiety.

Antimicrobial study

All the ligands and complexes were tested for *in vitro* antimicrobial activity. The antimicrobial activity values of the compounds against pathogenic gram-positive and gram-negative bacteria and fungi are presented in TABLE 2 & 3. The compound SFAP and SBAP showed poor antibacterial activity, while Co complexes showed good activity against *Pseudomonas aeuroginosa, E-coli, bacillus cereus, salmonella typhi, klebsilla pneumonia* bacteria. The antifungal activity of the compounds was studied with pathogenic fungi, and the results are given in TABLE 4. Ampotericin B is used as a reference. All the compounds showed significant antifungal activity, especially compound SBA-Co complex, has high activity than others. It was found that most of the synthesized compounds possess antimicrobial properties. The maximum activity was observed for the cobalt complexes.

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ABREVIATION

PA- *Pseudomonas aeuroginosa,*
EC- *E-coli,*
BC- *bacillus cereus,*
ST- *salmonella typhi*
KP- *klebsilla pneumonia*
A.O- *Aspergillus oryzae*
A.F- *Aspergillus fumigates*
MIC- minimum inhibitory concentration

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